Remarks

Before proceeding with discussion of the present amendment, Applicants wish to thank the Examiner for the attention given to this application at the interview. The Office Action mailed October 24, 2001, has been received and reviewed. Claims 1, 3-14, 17-19 and 22-25 are currently pending in the application. All claims stand rejected. In accordance with the discussion at the interview, Applicants have cancelled claims 3-14, 17-19 and 22-25 and present new claims 26-36, based upon the claims suggested by the Examiner. Reconsideration of the application as amended herein is respectfully requested.

Claim 1 was rejected in the Office Action under § 102(b) in view of de Groot N, van Kuik-Romeijien P, Lee SH, & de Boer, Over-expression of the murine polymeric immunoglobulin receptor gene in the mammary gland of transgenic mice, *Transgenic Research* 8: 125-135, 1999 (de Groot et al.). The filing date of the present application is July 21, 2000. Attached hereto as Exhibit A is a copy of a letter from Kluwer Academic Publishers B.V., the publisher of *Transgenic Research*. This letter provides the printing date of this issue of the journal as July 22, 1999 and the shipment date as August 3, 1999. A declaration from Herman Albert de Boer evidencing these dates, and identifying the material as Applicant's own work will be submitted to the Office.

A journal article or magazine is effective as a printed publication under 35 U.S.C. § 102(b) as of the date it reached the addressee and not the date it was placed in the mail. See, e.g., MPEP § 706.02(a) and § 2128 and *Protein Foundation Inc. v. Brenner*, 151 USPQ 561 (DDC 1966). The effective date for the de Groot et al. reference is thus well within one year of the filing date. Upon submission of the declaration Applicants respectfully submit this basis for rejection will be accordingly removed, and amended claim 1 and the newly presented claims are allowable.

Turning to the newly presented claims, these claims are based on those suggested by the Examiner, the differences from the claims suggested by the Examiner are supported by the specification and further clarify the scope of the present invention. Some elements of the newly presented claims will be discussed in view of the Office Action to show support for these changes.

In the Office Action at pages 8-10, claims directed to transgenic farm animals other than mice were rejected as not enabled under 35 USC § 112. The Office Action concludes that the state of the art of transgenics is not predictable with respect to transgene behavior and resulting phenotype. At

page 10, it states that it would require "an undue amount of experimentation to reasonably predict the results achieved in any other non-human farm animal besides mice comprising the expression of a protein (e.g. pIgR), the levels of the transgene product, the consequences of the production, and therefore, the resulting phenotype...." This conclusion is based on the citation of several references, Wall (1996), Houdebih (1994), Hammer et al. (1986), Ebert et al. (1988), Mullins (1996), Kappel (1992) and Strojeck & Wagner (1988), which are 14 to 4 years before the filing date of the application and list problems associated with obtaining transgenic animal in the 1980s and early 1990s.

Since this early work, novel techniques have been developed that successfully overcome the problems noted by the Office Action. These techniques have resulted in the obtaining of a high frequency of transgenic non-human farm animals, such as cows, that express desired proteins at predictably high levels. For example, yeast artificial chromosomes may be used to introduce large pieces of DNA bearing all the required transcription signals which are protected from position effects, (*See, e.g.*, Fujiwara Y, Analysis of control elements for position independent expression of human alpha-lactalbumin YAC, *Mol. Reprod. Dev.* 54 (1) pages 17-23, September 1999). In view of the state of the art at the time of the application, the newly presented claims to non-human farm animals should be considered enabled by the specification.

Further, it is customary for researchers contemplating the production of commercially interesting levels of any pharmaceutical protein in the milk of transgenic farm animals to test the gene constructs (expression levels, correctness of splicing, correctness of the function of the resulting protein, and so forth) first in mice, using a promoter to drive the expression of the gene that is of therapeutic interest. When a heterologous system (such as a bovine promoter) is used, as in the experimental section of the present specification, if expression levels achieved in transgenic mice are sufficiently high, they will be similarly high, if not higher, if such constructs are subsequently used in a homologous system (when transgenic cows are made with such constructs). *See, e.g.*, Krimpenfort et al., Generation of transgenic dairy cattle using in vitro embryo production technology, *Bio/Technology* 9 pages 844-847, 1991. As a general rule, eukaryotic mammalian promoters are not very selective in this respect, and will work between species. The high degree of homology between promoters or certain tissues among such species provides further support for the

ability to move from a mouse model to another non-human farm animal without undue experimentation.. Applicants thus respectfully submit that the claims are further enabled by the specification, and request they be allowed.

Returning to amended claim 1, the Office Action rejects this claim as lacking enablement under § 112 for the reasons discussed in the preceding paragraph, and further as not enabled for any immunoglobulin other than IgA or IgM. Applicants respectfully submit that, as amended, claim 1 is enabled with respect to transgenic non-human farm animals for the reason previously discussed herein. With respect to the enablement of specific immunoglobulins, claim 1 has been amended to reflect the encoded protein is a polymeric immunoglobulin receptor. As such a receptor is capable fo binding polymeric immunoglobulins, such as IgA and IgM, Applicant's respectfully submit that amended claim 1 is enabled and request it be allowed.

Copies of a sequence listing on paper and disk, with the statement required by the Office rules is submitted herewith, and Applicants respectfully submit that no further action is required on this point.

An Information Disclosure statement is being prepared and will be submitted to the Office to ensure all the references are considered.

CONCLUSION

The newly presented claims are believed to be in condition for allowance, and an early notice thereof is respectfully solicited. Should the Examiner determine that additional issues remain which might be resolved by a telephone conference, he is respectfully invited to contact Applicants' undersigned attorney

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Please replace the paragraph beginning at page 14, line 15 with the following replacement paragraph:

PCR analysis of tail DNA was performed with the upstream primer corresponding to a 16 bp sequence in the bovine a_{s1}-casein promoter region (5'-CTTGGGAGAGGAACTG-3' ([SEQ.I.D. NO. __] SEQ ID NO: 1)) and the downstream primer corresponding to a 21 bp sequence in exon 1 (5'-AGCTACTTCCTTCTCTCCAGG-3' ([SEQ.I.D. NO. __] SEQ ID NO: 2)) or a 21 bp sequence in exon 2 (5'-AAGACAGTTACCAAGAGCGTG-3' ([SEQ.I.D. NO. __] SEQ ID NO: 3)) of the pIgR gene. A PCR product of 234 bp was generated after 30 cycles (1 minute 94^{0}C, 1 minute 47^{0}C, 1 minute 72^{0}C) in case of integration of the c2pIgRE2 construct. A PCR product of 244 bp was generated after 30 cycles (1 minute 94^{0}C, 1 minute 50^{0}C, 1 minute 72^{0}C) in case of integration of the c1pIgRE1 construct. The PCR was performed in 50 ml containing 1 ml of tail DNA, 1.0 unit of Goldstar Red DNA polymerase (Eurogentec), reaction buffer (75 mM Tris-HCl, pH 9.0, 20 mM (NH4)2SO4, 0.01% (w/v) TWEEN 20, 1.0 mM MgCl2 ; Eurogentec), 0.5 mM of each primer and 0.2 mM dNTP (Gibco).

Please replace the paragraph beginning at page 14, line 29 and continuing to page15, line 23 with the following replacement paragraph:

Total RNA was extracted from the mammary gland and seven other tissues (heart, spleen, liver, intestine, salivary gland, kidney and uterus) using TRIzol Reagent (Gibco BRL) (Chomczynski et al., 1987). Transgene expression was measured at 8 or 12 days during the lactation stage. Northern blot analysis was performed according to standard protocols (Sambrook et al., 1989). Briefly, the RNA preparations were separated by electrophoresis under denaturing conditions in a 0.7% agarose MOPS/formaldehyde gel and transferred from the gel to HybondTM-N+ membrane (Amersham) by downward alkaline capillary blotting for 4 hours (Chomczynski, 1992). After

blotting, the membranes were pre-hybridized for 30 minutes in hybridization solution (0.125M Na2HPO4, 0.25M NaCl, 1.0mM EDTA, 7% SDS, 10% PEG 6000) with herring sperm DNA (Promega), followed by hybridization for 2 hours at 65^{0}C. The hybridization temperature for the synthetic oligonucleotide was 45^{0}C. The probes were labeled with [a-^{32}P] dCTP (3000 Ci/mmol, ICN) using the random primer DNA labeling kit (Gibco BRL). The synthetic oligonucleotide was labeled with [g-^{32}P] dATP (4500 Ci/mmol, ICN) using T4 polynucleotide kinase (Pharmacia). RNA blots were probed with an oligonucleotide (5'-ATCGATGGGTTGATGATCAAGGTGATGG-3' ([SEQ.I.D. NO. __] SEQ ID NO: 4)) corresponding to the complementary sequence of the bovine a_{s1}-casein 5'UTR (exon 1) to determine the expression level of the transgene (probe 3, FIG. 1D). Endogenous expression of the murine pIgR gene together with the transgene expression was measured with the murine pIgR cDNA (3095 bp) (Piskurich et al., 1995). Endogenous expression of a milk protein gene was measured with a 200-bp EcoRI-PstI murine b-casein cDNA fragment (Hennighausen et al., 1982). To correct for RNA loading differences, blots were hybridized with a 1.4 kb human 28S ribosomal probe. The transcription levels of the pIgR transgene in the different mouse lines were compared with the endogenous pIgR levels by measuring the hybridization signal with a Betascope 603 Blot Analyzer (Westburg b.v., the Netherlands).

IN THE CLAIMS:

Please amend claim 1 , and cancel claims 3-14, 17-19 and 22-25 and enter new claims 26-36, as follow.

1. (Three times amended) A method for raising the concentration of a first class of immunoglobulin relative to at least a second class of immunoglobulin in a compartment of a body of a transgenic non-human farm animal or progeny thereof said method comprising:

providing a mammary gland cell of a non-human farm animal with a nucleic acid encoding a [protein] polymeric immunoglobulin receptor capable of transporting a member of said first class of immunoglobulin from the mammary gland cell's basolateral side to the mammary gland cell's apical side; such that said nucleic acid is integrated into said mammary gland cell's genome.

26. (New) A transgenic farm animal having a genome, the genome comprising a recombinant nucleic acid encoding a polymeric immunoglobulin receptor (pIgR) protein, wherein said protein is capable of transporting an immunoglobulin protein across the basolateral side of an epithelial cell's apical side, resulting in over-expression of the immunoglobulin protein on the epithelial cell's apical side in comparison to another immunoglobulin protein located on the epithelial cell's basolateral side.

27. (New) The transgenic farm animal of claim 26, wherein the immunoglobulin protein is selected from the group consisting of IgM, IgA, IgG1 and IgG2.

28. (New) The transgenic farm animal of claim 26, wherein the immunoglobulin protein located on the epithelial cell's basolateral side is IgG.

29. (New) The transgenic farm animal of claim 26, wherein said transgenic farm animal over-expresses said pIgR protein at least 10-fold higher than the expression of the pIgR protein in the wild-type of said farm-animal.

30. (New) A method of making the transgenic farm animal of claim 26, said method comprising:

producing a DNA construct comprising a nucleic acid encoding a pIgR protein operably linked to a promoter capable of driving expression of said pIgR protein in an epithelial cell;

introducing said DNA construct into fertilized eggs; and

implanting the fertilized eggs comprising said DNA construct into a pseudopregnant female farm animal, thereby producing the transgenic farm animal according to claim 26.

31. (New) The method according to claim 30, wherein said promoter capable of driving expression of said pIgR protein in an epithelial cell is a casein promoter.

32. (New) A method of collecting an immunoglobulin from the transgenic farm animal

of claim 26, comprising:

providing a transgenic farm animal from claim 26, whose genome comprises a recombinant nucleic acid encoding a polymeric immunoglobulin receptor (pIgR) protein, which said protein is capable of transporting an immunoglobulin protein across the basolateral side of an epithelial cell to the epithelial cell's apical side, resulting in over-expression of the immunoglobulin protein on the epithelial cell's apical side compared to another immunoglobulin protein located on the epithelial cell's basolateral side; and

collecting milk comprising said immunoglobulin protein from the mammary gland of said transgenic farm animal.

33. (New) The method according to claim 32, further comprising isolating said immunoglobulin protein from the milk.

34. (New) The method according to claim 32, wherein collecting milk comprising said immunoglobulin protein comprises collecting milk comprising either IgM, IgA, IgG1 or IgG2.

35. (New) The method according to claim 31, comprising administering a protein capable of enhancing the expression of pIgR in the transgenic farm animal prior to collecting milk from the mammary gland, the protein selected from the group consisting of interferon-γ, interleukin-1, interleukin-4, and tumor necrosis factor-α.

36. (New) The method according to claim 31, comprising administering an antigen to said farm animal prior to collecting the milk from the mammary gland.